Contains Nonbinding Recommendations

Draft Guidance on Ferric Carboxymaltose

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Ferric carboxymaltose

Dosage Form; Route: Injectable; intravenous

Recommended Studies: Two studies

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1. **Type of study:** Fasting
   Design: Single-dose, randomized, parallel in vivo study
   Strength: 750mg/15mL (Dose: 750 mg)
   Subjects: Adult patients with iron deficiency anemia, for whom oral supplementation alone was not adequate or is not appropriate, and/or patients with non-dialysis dependent chronic renal disease.

   Additional Comments: The products should be administered undiluted as a slow intravenous push at the rate of approximately 100 mg (2 mL) per minute. Study subjects should have prescriptions for treatment with ferric carboxymaltose injections. Inclusion criteria should include at least: 1) body weight of 50 kg or above; 2) Hgb<12g/dL; 2) ferritin ≤ 100ng/mL or ≤300ng/mL when TSAT is ≤30%. Exclusion criteria should include at least: 1) pregnant or nursing females; 2) patients with known hypersensitivity to drug, excipients, or similar product; 3) clinically significant or labile hypertension; 4) significant comorbidities or concomitant medications that may affect PK results; 5) blood loss leading to hemodynamic instability; and 6) recent parenteral iron within the last 3-6 months.

   Analytes to measure (in appropriate biological fluid): Measure each of the following:

   1. [Total Iron] in serum
   2. [Transferrin-bound Iron] in serum

   Bioequivalence based on (90% CI): Total Iron

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2. **Type of Study:** particle size distribution
   Design: In vitro testing on at least three lots of both test and reference products
   Parameters to measure: Z-average size and Polydispersity Index (PDI)
   Bioequivalence based on (95% upper confidence bound): Z-average size and polydispersity index using the population bioequivalence statistical approach.

   Quartz cuvettes should be used for size characterization to avoid interference of plastic cuvettes with the intensity of the light scattered from the iron sucrose particles.

Waiver request of in vivo testing: Not Applicable.

Dissolution Method: Not Applicable.

Special considerations:

1. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD. Equivalence of stoichiometric ratios of iron, carboxymaltose, and other relevant components need to be established.

2. Sameness in physicochemical properties needs to be established. These in vitro characterizations should be conducted on at least three batches of the test and reference product. Attributes that should be included in the characterization are:
    - Iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment.
    - Composition of carbohydrate shell and surface properties.
    - Particle morphology.
    - Labile iron determination under physiologically relevant conditions. The tests can be performed with in vitro haemodialysis system, the catalytic bleomycin assay of spiked human serum samples, the spectrophotometric measurement of Fe reduction, or other methods that are validated for accuracy and precision.

3. For additional information regarding statistical analysis of in-vitro data, please refer to *Bioequivalence Recommendations for Specific Products: Budesonide Suspension (Draft)*.